LISBOA
UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA LISBOA

TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Laboratório de Farmacologia Clínica e Terapêutica

Thrombotic Events with Specific NOAC Antidotes: Systematic Review and Meta-Analysis

André Oliveira Rodrigues

ABRIL'2020

LISBOA
UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA LISBOA

TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Laboratório de Farmacologia Clínica e Terapêutica

Thrombotic Events with Specific NOAC Antidotes: Systematic Review and Meta-Analysis

André Oliveira Rodrigues

Orientado por:

Doutor Claúdio Virgílio Antunes David

ABRIL'2020

RESUMO

Introdução

Os NOACs são alternativas adequadas aos antagonistas da Vitamina K e parecem apresentar melhor perfil de segurança. No entanto, mesmo os doentes medicados com NOACs sofrem de eventos hemorrágicos. Doentes com hemorragia ativa podem beneficiar da reversão do efeito farmacológico dos NOACs apesar dos possíveis efeitos adversos, como, eventos trombóticos. Por isso mesmo, sumarizámos a evidência disponível sobre os antídotos específicos para os NOACs, nomeadamente, o Idarucizumab, o Andexanet alfa e o PER977. Após esta recolha, avaliámos a incidência de eventos trombóticos e mortalidade, aquando da utilização destes antídotos em doentes, com hemorragia ativa ou submetidos a cirurgia/procedimento invasivo.

Métodos

Esta revisão incluiu todos os estudos intervencionais publicados até Outubro de 2019 nas seguintes bases de dados: Cochrane Central Register of Controlled Trials, MEDLINE(R) e PsycINFO. Os estudos incluídos foram aqueles que descreveram doentes elegíveis para a administração do antídoto específico e que reportaram pelo menos um evento trombótico ou uma morte.

O risco de viés foi avaliado através de uma adaptação da *Critical Appraisal Skills Programme (CASP) Checklist*. Utilizou-se o *software Openmeta-analyst*, e os resultados encontram-se expressos em percentagens e com intervalos de confiança de 95% (CI). Foi usada a *Freeman-Turkey transformation (double arcsine transformation)*, de forma a estimar a frequência dos eventos, limitando o IC entre 0-100%. A heterogeneidade foi avaliada recorrendo ao I^2 *statistics*.

Resultados

Nove estudos, maioria estudos coorte, que reuniram um total de 1292 doentes, foram incluídos na revisão sistemática e meta-análise. Estudos sobre o PER977 não foram encontrados.

A análise combinada de eventos trombóticos incluiu cinco estudos e resultou numa incidência de 6,1% (95%CI 1.8–12.3%). Em relação à mortalidade, a análise combinada incluiu nove estudos e resultou numa incidência de 15% (95%CI 10.6–19.8%). Heterogeneidade moderada a alta foi observada em ambos os resultados.

Conclusão

O tratamento com Idarucizumab e Andexanet alpha reduz de forma marcada a atividade anti-trombina e anti-fator Xa, respectivamente, o que conduz a uma hemostasia eficaz nos doentes hemorrágicos. Apesar da eficácia destes fármacos, os doentes poderão sofrer de eventos trombóticos com uma incidência de 6.1%. Sendo que esta incidência é superior nos doentes que foram tratados com o Andexanet alpha.

Palavras-chave: NOAC antidotes; Idarucizumab (BI655075); Andexanet alpha (PRT064445); PER977; thrombotic events.

ABSTRACT

Introduction

NOACs are suitable alternatives to VKAs and seem to be safer. However, even patients under NOACs can have hemorrhagic events. Patients with acute bleeding may benefit from reversing the pharmacological effect of NOACs in addition to the standard measures, although the possible side effects, such as thrombotic events. Therefore, we reviewed the current evidence about specific NOAC antidotes, namely Idarucizumab, Andexanet alpha and PER977, evaluating the incidence of thrombotic events and mortality, when used in patients with active bleeding or undergoing urgent surgery or invasive procedure.

Methods

The review included all published interventional studies until October 2019 from Cochrane Central Register of Controlled Trials, MEDLINE(R) and PsycINFO. Studies, describing eligible patients for reversal with specific antidotes and that reported at least one thrombotic event or death, were included.

The risk of bias was assessed using an adapted Critical Appraisal Skills Programme (CASP) Checklist. Openmeta-analyst software was used, and the results were expressed in percentages (frequency) and 95%-confidence intervals (CI). Freeman-Turkey transformation (double arcsine transformation) was used to adjust the dataset to estimate the frequency of the events, limiting the CI among 0-100%. Heterogeneity was evaluated using the I^2 statistics.

Results

Nine studies with a total of 1292 patients were included in the review and meta-analysis, eight of them were cohort studies and one was case series. Studies about PER977 were not found.

Five studies were included in the thrombotic events pooled analysis with an incidence of 6.1% (95%CI 1.8–12.3%). Regarding all-cause mortality pooled analysis

included nine studies with an incidence of 15% (95%CI 10.6–19.8%). A moderate to high heterogeneity was observed in both outcomes.

Conclusions

The best available evidence indicates that even with the demonstrated effectiveness of the treatment with Idarucizumab and Andexanet alpha reducing anti-thrombin and anti–factor Xa activity, respectively, to achieve haemostasis, patients can suffer from thrombotic events with an incidence of 6.1%. This incidence was higher in patients who needed Andexanet alpha.

Keywords: NOAC antidotes; Idarucizumab (BI655075); Andexanet alpha (PRT064445); PER977; thrombotic events.

INDEX

INTRODUCTION

Non-vitamin K antagonist oral anticoagulants (NOACs), including direct thrombin inhibitor dabigatran and factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, can be used as a reliable alternative for vitamin K antagonists (VKAs). These anticoagulants help prevent strokes in patients with atrial fibrillation and are indicated to treat deep-vein thrombosis and pulmonary embolism and to prevent venous thrombosis, especially after orthopaedic surgery. NOACs have emerged as the preferred choice, particularly in patients with indication to start anticoagulant therapy.[1; 2]

All NOACs have a predictable effect (onset and offset) without need for regular anticoagulation monitoring.[1] Another positive aspect is that NOACs seem to be safer since the risk of major bleeding, namely intracranial haemorrhage, is significantly decreased.

Nevertheless, patients treated with NOACs can have severe bleeding events. These events are among the most common reason for withholding or ending oral anticoagulants. Anticoagulation-related bleeding is associated with an increased risk of death.[2] Patients with life-threatening bleeding while treated with NOACs may benefit from its reversal in addition to the standard measures. This reversal may have side effects, such as thrombotic rebound events.

Objective

1. The purpose of this systematic review is to evaluate the incidence of thrombotic events and all-cause mortality in patients being medicated with NOACs that were treated with specific antidotes, Idarucizumab, Andexanet Alfa and PER977, because of acute bleeding or need of urgent surgery or other invasive procedure, assessing these antidotes in relation to their safety profile.

METHODS

This systematic review has been developed based on Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines.[3]

Types of included studies

The systematic review included all published interventional studies, potentially randomized controlled trials, cohort and case series studies, both retrospective or prospective. Studies had to include patients with active haemorrhagic events or undergoing surgery/invasive procedure being treated with anticoagulants (dabigatran, apixaban, edoxaban, rivaroxaban or low-molecular-weight-heparin) and eligible for reversal with specific antidotes (Idarucizumab, Andexanet alpha and PER977). Studies had to report at least one thrombotic event or death, regardless of age, sex and comorbidities. Studies with healthy individuals, case reports and studies with less than 10 patients were excluded. Regarding study design, we kept our eligibility criteria broad, although we do not expect any published randomized controlled trials due to the nature of the condition evaluated.

Types of outcome measures

Our primary outcome was the proportion of thrombotic events occurring until discharge or within 30 days after the administration of the antidote. The secondary outcome was all-cause mortality during the same timeframe. Whenever data for this time stratum was not available, we chose the closest follow-up to retrieve data. Other outcomes reported were pulmonary embolism, deep vein thrombosis (DVT), systemic embolism, ischemic stroke, transient ischemic attack and myocardial infarction.

Search methods for identification of studies

We searched for studies in the following electronic databases: Cochrane Central Register of Controlled Trials, MEDLINE(R), PsycINFO; from inception until October 2019. The following keywords were used to search for relevant studies: “Idarucizumab”; “BI655075”; “Andexanet alpha”; “PRT064445”; “PER977”;

"Ciraparantag". The full search strategy is presented in the Table S1 in the Supplementary Appendix.

Data extraction, Evaluation and Synthesis

Two reviewers screened the titles and abstracts yielded by the searches against the inclusion criteria. Posteriorly, the reviewer read the full text reports and determined whether they meet the inclusion criteria. Also, the reviewer recorded the reasons for the exclusion of articles only at the full text screening stage. (Table S2 in the Supplementary Appendix)

The reviewers then extracted data from the individual studies identified for inclusion onto a pre-piloted form. This information included: **studies characteristics, namely -** study type (cohort studies or case series), year, length of follow-up, sample size; **participants characteristics -** age-mean year; type of medicated NOAC or other anticoagulant; cause for antidote; **intervention characteristics -** type of administered antidote; **outcomes -** all outcomes listed above were extracted. (Table 1 and 2)

Risk of bias was assessed using an adapted Critical Appraisal Skills Programme (CASP) Checklist.[4] (Table S3 in the Supplementary Appendix)

The Openmeta-analyst software was used to synthesize the results and to determine the pooled estimated frequency of thrombotic events and mortality.[5]

The results of the individual and pooled studies were expressed in percentages (frequency) and 95%-confidence intervals (CI). Freeman-Turkey transformation (double arcsine transformation) was used to adjust the dataset to estimate the frequency of the events, limiting the CI among 0-100%.[6]

The random-effects model of DerSimonian and Laird [7] was used by default as this approach is the simplest and most commonly used method for fitting the random effects model and is particularly useful for larger samples.[8] Statistical heterogeneity was assessed using I^2 (based on chi-squared statistic and its degrees of freedom), which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than to chance.

RESULTS

Electronic database search yielded a total of 603 published references. After removal of duplicates, screening of title and abstract and evaluation for full-text eligibility, we included 9 studies for analysis. Figure 1 shows the detailed results of the search strategy.

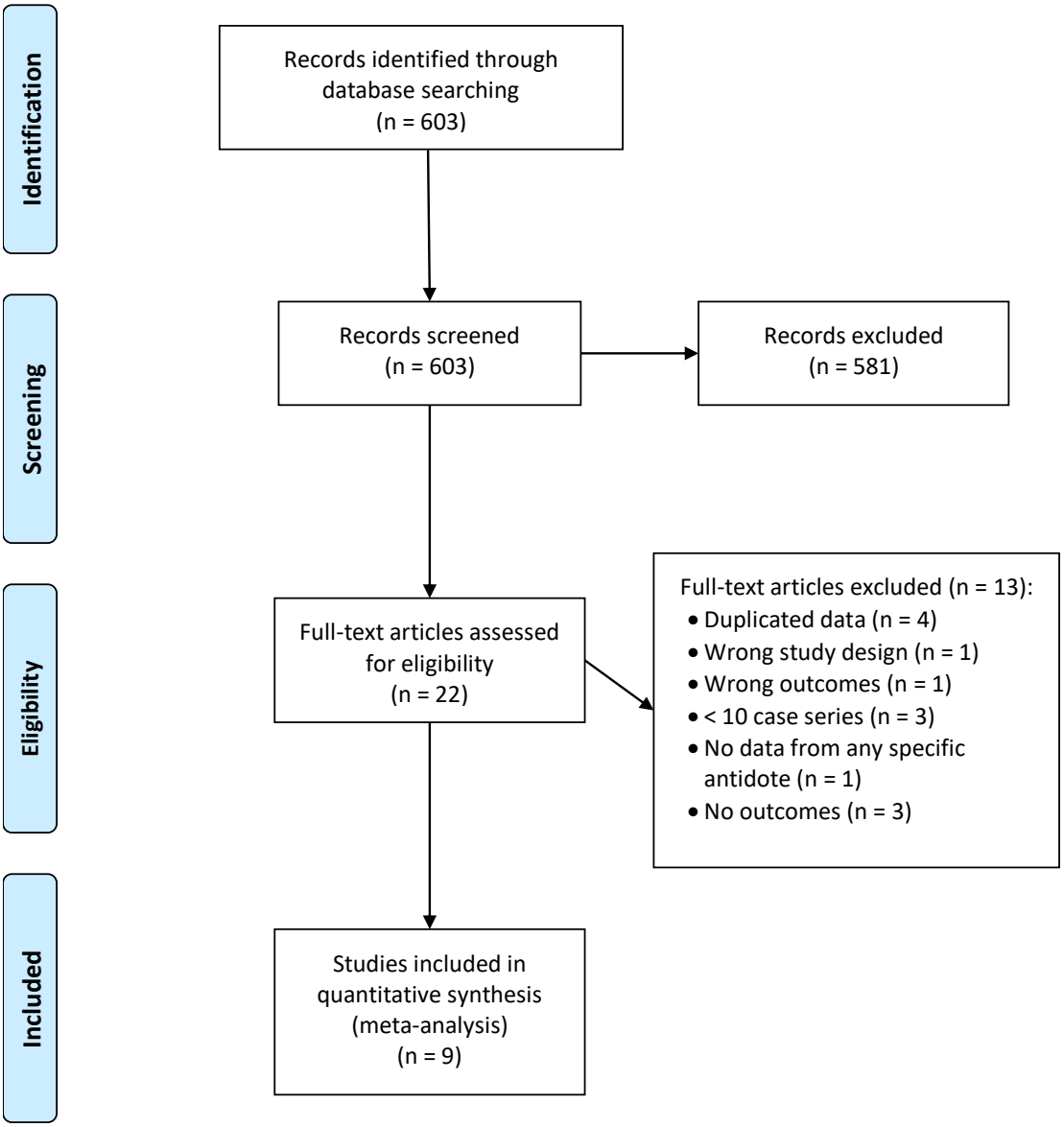

Figure 1. Flowchart of study selection.

Studies Characteristics

Of the 9 studies included in the review, 8 were cohort studies (two prospective and six retrospective) and 1 was case series (retrospective). The studies involved a total of 1292 patients, 1272 of them were being treated with NOACs and the remaining 20 with a low-molecular weight heparin (LMWH). The study that included the twenty patients taking enoxaparin was included in the review because of its sample size and importance. Two studies did not report mean age. In the other sudies, mean age of the patients varies between 75 years and 81 years. Follow-up ranged from hospital discharge to 3 months. The characteristics of the studies and patient population are presented in the Table 1 and 2.

Four studies only enrolled bleeding patients while in the other five studies both bleeding and undergoing surgery/invasive procedure patients were enrolled. Only one of the studies reported the use of the Andexanet alpha antidote, while in the others the antidote used was Idarucizumab. None of the included studies reported the use of PER977 antidote.

About our primary outcome, all thrombotic events, five studies had reported at least one event that was included in the meta-analysis. Regarding all-cause mortality, all studies presented data that was included in the meta-analysis, although with different follow-up times.

Proportion of Thrombotic Events

The pooled analysis included 5 studies and the incidence rate of thrombotic events in the patients treated with specific antidote was 6.1% (95%CI 1.8–12.3%) (Fig 2). A high heterogeneity (I^2=90.08%) was observed, with p-value <0.001.

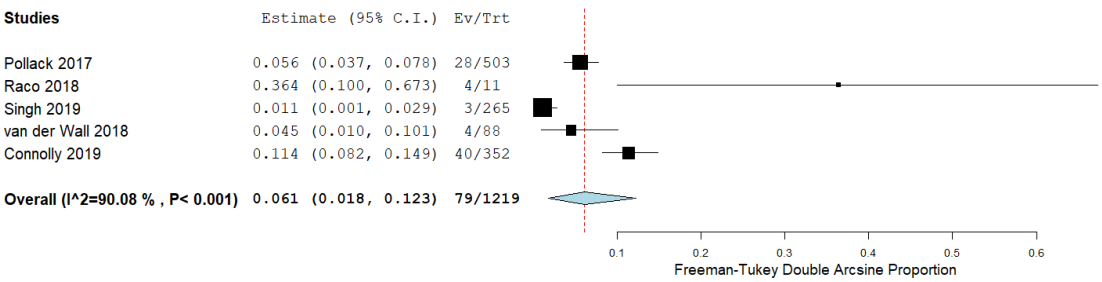

Figure 2. Forest plot with the proportion of thrombotic events with NOAC antidotes.

Proportion of All-cause Mortality

The pooled analysis included 9 studies and the incidence rate of all-cause mortality in the patients treated with specific antidote was 15% (95%CI 10.6–19.8%) (Fig 3). A moderate to high heterogeneity (I^2=65.07%) was observed, with p-value =0.003.

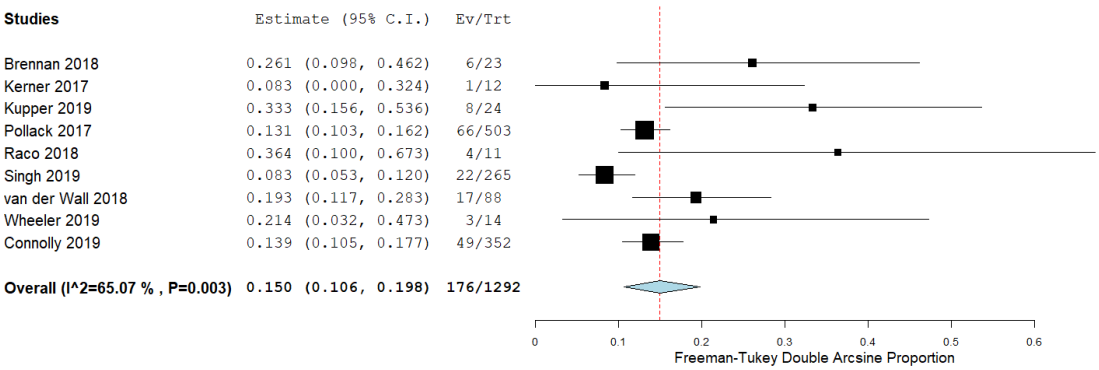

Figure 3. Forest plot with the proportion of all-cause mortality with NOAC antidotes.

Table 1. Main characteristics of included studies

Reference	Year	Type of study	Total patients	Age-mean year	Patients' NOAC	Cause for antidote	
						Bleeding	Undergoing surgery/invasive procedure
Brennan[9]	2018	Retrospective Cohort	23	77	Dabigatran	17	6
Kermer[10]	2017	Retrospective Case series	12	75	Dabigatran	12	0
Kupper[11]	2019	Retrospective Cohort	24	ND for these patients	Dabigatran	24	0
Pollack[12]	2017	Prospective Cohort	503	78	Dabigatran	301	202
Raco[13]	2018	Retrospective Cohort	11	81	Dabigatran	5	6
Singh[14]	2019	Retrospective Cohort	265	ND	Dabigatran	265	0
van der Wall[15]	2018	Retrospective Cohort	88	76	Dabigatran	53	35
Wheeler[16]	2019	Retrospective Cohort	14	ND for these patients	Dabigatran	11	3

Connolly[17]	2019	Prospective Cohort	352	77	Rivaroxaban	128	0
					Apixaban	194	0
					Edoxaban	10	0
					Enoxaparin	20	0

***ND**: Not described*

Table 2. Antidote used, follow-up and outcomes.

Reference	Total patients	Antidote used	Follow-up time after infusion	ATE	PE	DVT	SE	IS	MI	TIA	Non-specific VTE	All-cause Mortality
Brennan[9]	23	Idarucizumab	Until discharge	0	-	-	-	-	-	-	-	6
Kermer[10]	12	Idarucizumab	Until discharge	NR	NR	NR	NR	NR	NR	NR	NR	1
Kupper[11]	24	Idarucizumab	90 days	NR	NR	NR	NR	NR	NR	NR	NR	8
Pollack[12]	503	Idarucizumab	30 days	28	6	7	2	7	6	-	-	66
Raco[13]	11	Idarucizumab	90 days	4	-	2	-	2	-	-	-	4
Singh[14]	265	Idarucizumab	Until discharge	NR	NR	NR	NR	NR	NR	NR	NR	22
			30 days	3	-	-	-	-	-	-	3	NR
van der Wall[15]	88	Idarucizumab	90 days	4	2	-	-	2	-	-	-	17
Wheeler[16]	14	Idarucizumab	30 days	NR	NR	NR	NR	NR	NR	NR	NR	3
Connolly[17]	352	Andexanet alpha	30 days	40	5	13	-	14	7	1	-	49

***NR**: Not reported; **ND**: Not described; **ATE**: All thrombotic events; **PE**: Pulmonary embolism; **DVT**: Deep venous thrombosis; **SE**: Systemic Embolism; **IS**: Ischemic Stroke; **MI**: Myocardial infarction; **TIA**: Transient Ischemic Attack; **VTE**: Venous thromboembolism*

DISCUSSION

Nowadays it is accepted that strategies to manage bleeding complications in patients treated with NOACs rely on a precise analysis of their clinical status. First, the type of bleeding or the type of surgery/invasive procedure. Second, the patient and his/her previous treatment: the exact time of last NOAC intake, prescribed dosing regimen, renal function, factors influencing plasma concentrations and other factors influencing haemostasis, such as concomitant use of antiplatelet drugs.[1] This analysis is crucial in order to prevent inappropriate antidotes usage and to better select the treatments proposed for these patients and the possible side effects.

In this systematic review and meta-analysis, we showed that Idarucizumab and Andexanet alpha can be viable solutions for the patients mentioned above and even for patients medicated with a low-molecular-weight-heparin in the case of the only study with Andexanet alpha. We did not find any studies about PER977 that could be included in the review. This antidote was designed to reverse both direct thrombin and factor Xa inhibitors as well as the indirect inhibitor enoxaparin, binding in a similar way to each of them, something that is worth further research. [18, 19]

After the assessment of the included studies, eight of them on Idarucizumab and the remaining one about Andexanet alpha, we obtained the following incidences. The incidence rate of thrombotic events was 6.1% (Fig 2), which sum up the occurrence of 79 events between a total of 1219 patients, while all-cause mortality incidence was higher, 15% (Fig 3), which sum up the occurrence of 176 deaths between a total of 1292 patients. For both outcomes the heterogeneity of studies was high, resulting in wide CIs. The incidences of our primary and secondary outcomes were different and preclude a relation of direct association.

According Pollack et al., thrombotic events can be related with a low rate of reinitiating anticoagulation. Since thrombotic events that occurred within the first 72h were in patients that do not restart anticoagulation and the subsequent events were more likely to reflect the underlying prothrombotic state than to be a direct effect of reversal. For example, Idarucizumab had no procoagulant activity when it was given to animals and healthy human volunteers and was successfully used in patients on dabigatran presenting major bleeding, or with the necessity of urgent surgery or intervention.[12, 20, 21]

The study by Pollack et al. along with Singh et al. study gather the majority of the sample on Idarucizumab, together they present data of 768 patients in which this antidote was administered in patients under dabigatran.

The vast majority of patients that underwent surgery were reported in the Pollack et al. study, which together with the remaining surgical patients in the other studies, showed a percentage of thrombotic events of 4.8%.

In the study by Connolly et al, with a total of 352 patients, it was described that most events occurred in patients which resumption of oral anticoagulation was delayed or in patients who did not restart anticoagulation, reinforcing the premise that using this antidotes is not directly related to thrombotic events. After restarting of oral anticoagulation, no patient had a thrombotic event during the 30 day follow-up.[17] Because of this a recent European Society of Cardiology (ESC) consensus recommends NOACs resumption after major bleeding as soon as the thrombotic risks outweigh the re-bleeding risks, in most cases within one week.[15]

Regarding all-cause mortality, in the study by Pollack et al., most deaths that happened within 5 days after admission seem to be related to the severity of the bleeding event or to coexisting conditions (e.g., respiratory failure or multiple organ failure), whereas deaths that occurred after 30 days were more likely to be independent events or connected to coexisting conditions.[12] Thus, supporting the hypothesis that thrombotic events are not directly related to mortality rates.

The conditions in which acute major bleeding is associated with the use of thrombin and factor Xa inhibitors are medical emergencies with a poor prognosis. There are limited treatment options for such patients.[17] Not only for that reason, our results are important for clinicians and investigators as they expose the most recent and significant data about the use of Idarucizumab and Andexanet alpha. These reversals have demonstrated quality and effectiveness in bleeding control in patients under NOACs or even other anticoagulants such as enoxaparin, thus promoting the need to further and more complete investigation on these drugs and their side effects.

Our findings support the need to add some information in future studies, such as, more accurate monitoring during follow-up for these patients with blood tests to monitor the presence and evolution of NOACs and complete descriptions of the thromboembolic events and associated mortality. This kind of surveillance would be helpful to monitor the effectiveness of these antidotes for acute haemorrhagic events or

undergoing surgery/invasive procedure and to further assess its safety. A limitation of our study was the difference between follow-up times in the studies.

It would be advantageous to use RCTs to study these effects, but this study strategy cannot be applied to our highly vulnerable population mainly because of logistic and ethical challenges, given the perceived risks of placebo assignment in this.

CONCLUSIONS

The best available evidence indicates that even with the demonstrated effectiveness of the treatment with Idarucizumab and Andexanet alpha reducing anti-thrombin and anti–factor Xa activity, respectively, to reach haemostasis, patients can suffer from thrombotic events with an incidence of 6.1%. This incidence was higher in patients who needed Andexanet alpha.

The incidence above along the 15% incidence of all-cause mortality, it is possible to realize that regardless of whether these findings reflect a delayed or not restarted anticoagulation, the underlying severity of disease or even the exposure to these antidotes, clinicians should remain vigilant and consider close monitoring and follow-up of these patients.

BIBLIOGRAPHY

1. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-Vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J*. 2018;39(16):1330-1393. doi:10.1093/eurheartj/ehy136

2. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med*. 2015;373(25):2413-2424. doi:10.1056/NEJMoa1510991

3. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. doi:10.1136/bmj.b2700

4. Critical Appraisal Skills Programme (CASP). CASP Checklist: Cohort Study. *Casp Uk*. 2018;(2018):7. www.casp-uk.net.

5. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P SC. Closing the Gap between Methodologists and End-Users: R as a Computational Back-End. *J Stat Softw*. 2015;49(5):1-15. doi:10.18637/jss.v049.i05

6. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health*. 2013;67(11):974-978. doi:10.1136/jech-2013-203104

7. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Stat Med*. 1986;188:177-188. doi:10.1016/0197-2456(86)90046-2

8. Jackson D, Bowden J BR. How does the DerSimonian and Laird procedure for random effects meta-analysis compare with its more efficient but harder to compute counterparts? *J Stat Plan Inference*. 2010;140(4):961-970. doi:10.1016/j.jspi.2009.09.017

9. Brennan Y, Favaloro EJ, Pasalic L, Keenan H, Curnow J. Lessons learnt from local real-life experience with idarucizumab for the reversal of dabigatran. *Intern Med J*. 2019;49(1):59-65. doi:10.1111/imj.13995

10. Kermer P, Eschenfelder CC, Diener HC, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany – A national case collection. *Int J Stroke*. 2017;12(4):383-391. doi:10.1177/1747493017701944

11. Küpper C, Feil K, Klein M, et al. Idarucizumab administration in emergency situations: the Munich Registry of Reversal of Pradaxa® in clinical routine (MR REPAIR). *J Neurol*. 2019;266(11):2807-2811. doi:10.1007/s00415-019-09492-w

12. Pollack C V., Reilly PA, Van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377(5):431-441. doi:10.1056/NEJMoa1707278

13. Raco V, Ahuja T, Green D. Assessment of patients post reversal with idarucizumab. *J Thromb Thrombolysis*. 2018;46(4):466-472. doi:10.1007/s11239-018-1723-1

14. Singh S, Nautiyal A, Belk KW. Real World Outcomes Associated with Idarucizumab: Population-Based Retrospective Cohort Study. *Am J Cardiovasc Drugs*. 2019;(0123456789). doi:10.1007/s40256-019-00360-6

15. Van Der Wall SJ, Van Rein N, Van Den Bemt B, et al. Performance of idarucizumab as antidote of dabigatran in daily clinical practice. *Europace*. 2019;21(3):414-420. doi:10.1093/europace/euy220

16. Wheeler M, Borrie A, Dookia R, Carter J. Idarucizumab for dabigatran reversal: the first 6 months in a tertiary centre. *Intern Med J*. 2019;49(10):1316-1320. doi:10.1111/imj.14459

17. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380(14):1326-1335. doi:10.1056/NEJMoa1814051

18. Crowther M, Crowther MA. Antidotes for novel oral anticoagulants: Current status and future potential. *Arterioscler Thromb Vasc Biol*. 2015;35(8):1736-1745. doi:10.1161/ATVBAHA.114.303402

19. Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med*. 2014;371(22):2141-2142. doi:10.1056/NEJMc1411800

20. Glund S, Stangier J, van Ryn J, et al. Effect of Age and Renal Function on Idarucizumab Pharmacokinetics and Idarucizumab-Mediated Reversal of Dabigatran Anticoagulant Activity in a Randomized, Double-Blind, Crossover Phase Ib Study. *Clin Pharmacokinet*. 2017;56(1):41-54. doi:10.1007/s40262-016-0417-0

21. Glund S, Moschetti V, Norris S, et al. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. *Thromb Haemost*. 2015;113(5):943-951. doi:10.1160/TH14-12-1080

SUPPLEMENTARY DATA

Thrombotic Events with Specific NOAC Antidotes: Systematic Review and Meta-Analysis

Table S1 – Detailed search strategy.

#	Searches
1	Andexanet.af.
2	PRT064445.af.
3	PER977.af.
4	Ciraparantag.af.
5	BI655075.af.
6	Idarucizumab.af.
7	1 or 2 or 3 or 4 or 5 or 6

Table S2 – Detailed reasons for exclusion at full text screening stage.

Bernstein 2016	Duplicated data.
Calabria 2018	Wong study design - the study only identifies a representative sample of patients potentially eligible to the specific reversal agent on the market, Idarucizumab.
Connolly 2016	Duplicated data.
Fanikos 2019	Wrong outcomes - the study only provides information how a NOAC reversal agent is used in the real-world setting, examining where Idarucizumab is prescribed (across regions and within hospitals), the patients who received Idarucizumab, and why they received it.
Levy 2019	Duplicated data.
Oberladstatter 2019	No outcomes - Both thrombotic events and mortality were not reported until discharge.
Okishige 2019	No outcomes - After 30 day of follow-up there were no thrombotic events or mortality reported.
Pollack 2017	Duplicated data.
Sheikh-Taha 2018	No outcomes - Both thrombotic events and mortality were not reported until discharge.
Testa 2018	< 10 case series - the study only shows 3 cases where Idarucizumab was administered due to bleeding and even these doesn't specify the necessary outcomes.
Thringh-Duc 2016	No data from any specific antidote - the article only tries to compare the spontaneous report of Dabigatran adverse effects in the French pharmacovigilance database with the adverse effects reported in an Idarucizumab clinical trial.
Vosko 2017	< 10 case series - the study only includes 8 patients with bleeding or undergoing surgery/invasive procedures.
Sowerby 2019	Wrong outcomes - the study does not report any outcomes.

Table S3 - CASP case-cohort study checklist.

	Brennan[9]	Kermer[10]	Kupper[11]	Pollack[12]	Raco[13]	Singh[14]	van der Wall[15]	Wheeler[16]	Connolly[17]
1.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	Yes
3.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
4.	Yes	Yes	Yes	Yes	Can't tell	Can't tell	Yes	Yes	Yes
5. (a)	Yes (renal impairment)	Yes (small sample)	Yes (small sample)	Can't tell	Yes (small sample)	Yes (disease severity)	Yes	Yes (small sample)	Yes (different bleeding source)
5. (b)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. (a)	Yes	No	No	Yes	Yes	No (sparse data)	Yes	No	Yes
6. (b)	No (just until discharge)	No (just until discharge)	Yes	Yes	Yes	Yes	Yes	Yes	Yes